REMARKS

Status of the Claims

Claims 1 and 7 are pending. Claims 1 and 7 are rejected. Claim 1 is amended herein. Claims 2-6 and 8-22 are canceled. No new matter has been added.

Claim amendments

Claim 1 is amended to delete the phrase "such that the tumor growth porbability approaches one". No new matter was added in this amendment.

The 35 U.S.C. §112, first paragraph, rejection

Claims 1 and 7 are rejected under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

The Examiner states that the specification, while being enabling for a method for sequentially reducing the size of a solid cancer greater than 1 mm in sized, does not reasonably provide enablement for a method that sequentially reduces the size of a solid cancer greater than 1 mm in size "such that the tumor growth probability approaches one".

Applicants have deleted this phrase from claim 1, so that step d) in amended independent claim recites that each sequential reduction in the size of the solid tumor increases the probability of remission in the individual. Applicants strongly aver that the instant specification enables a method of increasing the probability of remission with every layer of tumor cells removed with the instant bismuth-213/antibody constructs (pg. 19, ll. 6 to pg. 20, ll. 12) and that such an increase in probability is not possible without the high specific activity constructs. As is known in the art, remission is a state or period during which the symptoms of a disease are abated, such as occurs when a tumor is not detectable. The specification defines remission as the attainment of a complete response, i.e., reducing the tumor to a size less than 1 gm or 10^9 cells which is the limit of detectability (pg. 18, ll. 4-9).

Thus, an inventive concept of the instant application is determining a minimum high specific activity for a Bi-213-antibody construct effective to remove sufficient layers of cells over sequential periods of treatment such that the likelihood of a remission increases with every removal, i.e., to approach reducing the tumor to less than 1 gm and, optimally, to a durable remission. As amended, the scope of the claim does not include an absolute achievement of a durable remission or cure. As demonstrated in the specification, high specific activity is required for a minimum of 1 alpha particle from at least one of 2 Bi-213 atoms to be delivered to each cell to kill it. A single alpha particle could easily kill more than one cell since the average diameter of a tumor cell is 10-20 microns and the

range of an alpha particle is 40-80 microns. This is demonstrated by the removal of multiple layers of cells from a spheroid model of prostate cancer as discussed further *infra*. An antibody construct with a lesser specific activity is insufficient to kill enough tumor cells, even with multiple administrations, to increase the chances of remission.

Applicants have demonstrated that a bismuth-213/PSMA antibody construct eliminated 5-6 layers of cells in a spheroid model of prostate cancer with a single dose (pg. 39, ll. 5-17). The Examiner has stated that a spheroid model would not represent solid cancers in nature which are expected to be heterogeneous and contain cells that express antigens at different levels even from a single tumor. Amended claim 1 recites a range of high specific activities for Bi-213 of 10 mCi/mg to 30 mCi/mg and the specification teaches that for a tumor cell with approximately 10,000 binding sites, 10 mCi/mg of Bi-213 are required at a saturating dose of about 0.05-2.5 mg of antibody (pg. 16, ll. 14 to pg. 17, ll. 1). Applicants respectfully submit that this guideline would be readily useful to a person having ordinary skill in this art in determining other specific activities and doses for other binding sites.

Even though a tumor may express antigens heterogeneously, the scope of claim 1, as amended, encompasses increasing the probability of achieving remission which allows that not all tumor cells are killed. Remission occurs when a tumor is less than 1 gm, the duration of remission depends on how

much less than 1 gm the tumor is. It would not require undue experimentation nor be a burden for one of ordinary skill in the art to increase the high specific activity and/or the dose within the guidelines given in the specification. The specification further demonstrates how to determine the LD50 for HL60 cells with approximately 10,000 binding sites, which is about 2-2.5 initial atoms per cell, using easily obtainable cytotoxicity data. Applicants respectfully submit would not require undue experimentation and is well within ordinary skill to determine the initial atoms per cell for other cancer cell lines using different Bi-213 antibody constructs via these cytotoxicity assays (pages 39-42; Figures 3A and 4A).

The data in Example 12 demonstrate a significant reduction in PSA levels in mice with LnCaP tumors 3-5 mm in diameter after a single course of treatment. Given that the specification discloses that repeated administrations of Bi-213 is required to increase the probability of remission, sufficient guidance is provided for one of ordinary skill in the art to administer at least another course of treatment with the expectation that any residual tumor would be further reduced in size because a Bi-213 antibody construct of sufficiently high specific activity and dose can be prepared.

Respectfully, the Applicants disagree with the Examiner's statement interpreting the results in Example 13 as that cancer death does occur after 54 days in LnCaP-inocculated mice treated with four daily doses of Bi-213-J591, as compared to 31 days of the innoculated non-treated control. First, Applicants'

specification demonstrates that a dose of Bi-213-J591 antibody delivered as a 1 time dose or divided into four daily doses are equivalent. It is well-known in the art that a determined dose of a radionuclide can be administered as partial doses. Second, Applicants have demonstrated that a single course divided among four daily doses significantly increased the tumor-free survival time among LnCaP injected mice. Effectively, as discussed *supra*, the LnCaP mice in these Examples have only received an initial dose of Bi-213. Applicants submit that the data disclosed in Example 13 and shown in Figure 6 demonstrates that 50% of injected mice treated with Bi-213-J591 antibody were alive and tumor free up to day 51 after only a single dose of Bi-213-J591 and 50% were alive with tumors. Thus, as the Examiner states, this demonstrates prolonging tumor-free survival time, that is, a remission because the inference to be drawn from tumor-free is no detectable tumors. Although tumor-bearing control mice probably would die eventually from the cancer burden, if not subsequently treated as demonstrated in Example 12, one cannot predict that the surviving tumor-free mice would even eventually develop tumors absent continued monitoring.

Applicants results from these murine models demonstrates statistically significant therapeutic efficacy in increasing the probablity of remission. It is a probability of response in a population of tumor cells or in an individual. Predicting whether an individual will respond to the treatment with 100 certainty does not fall within the scope of the claims, as amended. In the art no one can predict with 100% certainty whether an individual will respond to any

drug. However, even though clinical efficacy is not required for patentability, Applicants wish to state that remissions in individuals have been achieved using this treatment modality.

Therefore, Applicants respectfully submit that the specification is enabling for the claims as amended herein. Accordingly, in view of the claim amendment and arguments presented herein, Applicants respectfully request that the rejection of claims 1 and 7 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §112, second paragraph, rejection

Claims 1 and 7 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

The Examiner states that claims 1 and 7 are indefinite for the use of the language "the tumor growth probability approaches one" in claim 1 as it is not clear what the phrase means. Applicants have deleted the phrase from claim 1. Accordingly, in view of this claim amendment, Applicants respectfully request that the rejection of claims 1 and 7 under 35 U.S.C. §112, second paragraph, be withdrawn.

This is intended to be a complete response to the Final Office Action, mailed October 31, 2006. Applicants submit that claims 1 and 7, as

presented herein, are in condition for allowance. Accordingly, Applicants request that claims 1 and 7 be passed to issuance.

If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants believe no fees are due, however, should Applicants err, please debit any applicable fees from Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

Date: April 30, 2007

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